**Claim Rejections – 35 USC § 112.**

Claims 1, 4-14, 20-25, 39-42, 48-50 stand rejected under 35 U.S.C. Section 112, first paragraph, for lack of enablement.

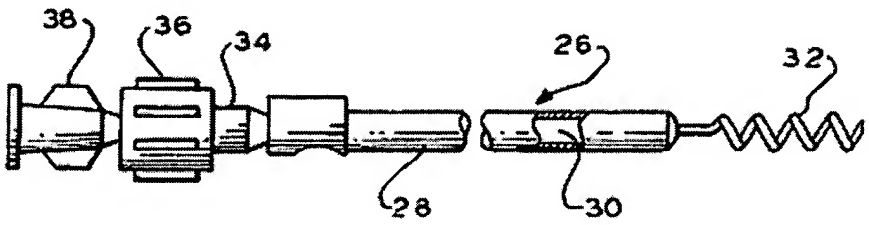
The Examiner had previously found that the specification does not provide an enabling disclosure for the delivery of therapeutically effective amounts of any conduction protein to cardiac tissues using any genetic material including nucleic acid vectors such that any effect on cardiac conduction is observed. The rejection under 112 was indicated to be based on "how to use" the invention as disclosed in the instant specification. 35 U.S.C. 112, first paragraph.

Applicants traverse. The examiner appears to essentially on two grounds that the invention is not enabled: (1) methods are essentially inadequate to deliver and transfect genes to cardiac tissue; and (2) the teachings are inadequate to effectively teach one skilled in the art of how to deliver connexins for their intended purpose.

In regard to the first issue, applicants believe there are presently adequate methods and systems for delivery of genetic agents to the heart. For example, enclosed is a copy of US Patent 5,797,870 (herein also referred to as the '870 patent), issued 8/25/1998, and correspond PCT application, WO 9639830, published 12/19/1996. Issued Claim 1, is as follows:

> 1. A method for delivering a **gene therapy agent to epicardial and pericardial tissue** of a **patient's heart**, comprising; providing an **elongated intravascular device having a distal tip configured to pierce a wall of the patient's heart**; guiding the distal tip of the device into the left ventricle of the patient's heart; **piercing the endocardium, the myocardium and the epicardium with the distal tip of the device**, said distal tip being located in the pericardial space; **introducing the gene therapy agent** through the distal tip; and; maintaining the **gene therapy agent** within the pericardial space for a sufficient period of time. **[emphasis added]**

Copy of the catheter device from the '870 patent is pictured below:




The US patent office believes in view of the '870 patent that one would prior to the date of the invention would be able to perform the transfection and transduction methods and procedures claimed and described therein using a helical screw in tip. Applicants fail to see how, in regard to the first part of the issue, that the Examiner can still maintain her position. The examiner has contented at length how introduction of genetic vectors is not possible in the heart, and that the state of the art fails to appreciate the difficulties of doing so. The Examiner appears to holding the patentee to beyond the legal standard, essentially requiring all problems must be solved to obtain FDA approval. That is not the legal standard, nor does it appear to be the general position of the US patent office.

In regard to the second issue, a lot has been stated as fact regarding the deficits of the specification. These statements merit further examination. First, the examiner indicates the specification only provides "prophetic examples for the isolation and purification of connexin cDNA into plasmids and adenoviral vectors", and "fails to provides any guidance as to the identity, sequence, or biological properties of any conduction proteins other than the connexin family members listed above (Cx40, Cx43, Cx45).

The applicants respectfully submit the claims were last amended to recite:

"recombinant nucleic acid vectors encoding a conduction protein selected from the group Cx40, Cx43, and Cx45" [amendment of August 31, 2001]

The Examiner appears to be rejecting the claims, but is rejecting that which is beyond the scope of the claims. Applicants respectively submit, that the structure, and purification of connexin genes is known, as well as method for preparing vectors containing them are well known. Examiner is well aware of the teachings of Kanter (J. Mol. Cell Cardiol., 1994, 26, 861-868),

Gourdie, et al. (J. cell Sci., 1993, 105, 985-991), and Fishman, et al., J Cell Biol, 1990, 111, 589-589). Applicants claims are fairly based as to the scope of connexins they are claiming – Cx40, Cx43, and Cx45. They are not claiming they discovered connexins. That teaching is in the art.

Applicants invention is directed to a system that allows people to know where to place conductive proteins in the heart, and to provide them guidance that after the have transfected the cells of the heart whether and to what degree they have been effective. This is possible by the fact that the claimed catheter system contains cardiac mapping and sensing elements that tells them as a base line what tissues may need transfection, and how to titrate or measure the effectiveness of their transfection by the ability to sense and measure any changes in cardiac conductivity by mapping the myocardium.

The Examiner also appears to contend that applicants only mode of transfection described is by electroporation:

> "In regards to the use of vectors such as viral or adenoviral vectors disclosed by the specification, the specification fails to provide essential teaching on the methods of delivery of genetic material from said catheter delivery device such that any electrical energy generated by the device would not adversely impact the ability of vectors to transduce cells in the cardiac tissue of damage the vector's stability and ability to transduce cells in the cardiac tissue or damage the vector's stability and ability to express the encoded transgene. The specification does not disclose to what extent the administration of an electric field from the applicant's device will effect the quantity, structural integrity, and biological properties of DNA or RNA delivered into the cells as a result of any increase in the permeation of the cell membrane. It is well known in the art that the administration of an electric field, such as in the use of electroporation, can result in a significant level (e.g. 40-80%) of cell lysis (e.g. See Weaver et at., US Patent 5,019,034, column 3, lines 44-64). The specification also fails to disclose the manner and ability of any genetic material to transduce cardiac tissue cells which have been damaged due to the use of a helical electrode which is screwed into the myocardium."

Applicants specification on page 20, third full paragraph, discusses a number of transfection methods, one which includes electroporation. However, electroporation is but one of the transfection techniques described. On page 21, first full paragraph, specifically describes in vivo treatment of cells. The described methods don't even refer to electroporation. The

Examiner seems to be reading issues into the claims based on a false presumption that electroporation methodology is the only method described for transfecting cells. Applicants due intend to claim the use of their mapping catheter with any technique that is effective for transfection or transduction of the cardiac cells, however, the examiner seems to be saying all techniques are ineffective.

Applicants also draw the attention to portions of the specification where therapeutically effective amounts of adenovirus are discussed (page 25, at the bottom of the page) as providing a bolus of virus: "Where adenovirsus vectors are used, the amount of recombinant nucleic acid molecule is preferably between $10^8$ pfu and $10^{14}$ pfu, and most preferably between $10^9$ pfu and $10^{12}$ pfu. The point of raising this matter is that if you compare the effective amounts used in the Maurice article it was $5 \times 10^{11}$ adeno-viral particles which is inside the preferred ranges given in the specification.

As to the last issue brought up by the Examiner in the last highlighted paragraph, the Examiner seems to be doubting the precedence of the US patent office in these matters for use of helical electrodes for transfection. Applicants, don't think this is the case, but want to make sure that the Examiner understands that applicants are claiming the use of mapping electrodes as part of the delivery system, and that somehow the Examiner isn't confusing this to be the same as using electrodes in an electroporation system? It is not.

With due respect, the Examiner continues at length to document various problems that others have had, suggesting in essence that years of research will be required before any patentable advances in this area are forth coming. In essence the Examiner believes that the patentees must solve all problems for FDA approval before they will be granted a patent. It is respectfully suggested this is not the law.

One of applicants contribution to the art is that they provide an effective delivery system to effectively delivery genes to cardiac cells that affect conduction. The delivery systems of the art will be advanced by the presence of a conduction mapping system, so that baseline readings of the heart can be made as to where to effectively delivery these genes, as well as to gage and monitor effect on transfection. As the Examiner knows, there are well know groups of proteins

that that affect conduction in the heart – connexins, and ion channel proteins. Applicants have applications covering these two aspects which were filed on the same day, yet they are receiving almost irreconcilable reviews in prosecution. Applicants direct the Examiner to US 6,567,705 and US 6,665,563. Applicants have successfully issued patents relating to the use of their delivery system for ion channel proteins, yet the instant case appears to be rejected out hand as not even remotely enabled in relation to connexins. Applicants wish to point out both cases were originally filed on the same day by Applicants.

The Examiner in the first full paragraph on page 6, seems to indicate that applicants specification provides no guidelines relating to the biophysical properties, or differences in tissue expression required for functional cardiac tissue:

> In addition to the lack of guidance concerning the identity of conduction proteins for use in the instant invention other than connexins, the identity of genetic material other than nucleic acid vectors, the effects of the claimed catheter delivery device on the ability of the cardiac tissue to take up foreign genetic material and the effects of the device on the ability of the genetic material to express any encoded protein as noted above, the specification fails to provide guidance as to the level of cardiac cell transformation, the types of cardiac cells transformed, and the level of expression of any conduction protein from any delivered genetic material that correlates with any effect on conduction in cardiac tissue in vitro or in vivo. The specification's sole disclosure of conduction proteins are members of the connexin family. At the time of filing, Kanter et al. discloses that the three members of the connexin gap junction family, Cx40, Cx43, and Cx45, have different biophysical properties, and that in combination they are believed to be important in the regulation of cellular coupling. Further, these proteins have regional differences in expression with the various cardiac tissues, such as the Purkinje fibers and ventricular myocytes, and they are not expressed in one-to-one-to-one ratios with any cardiac tissue (Kanter et la., page 861 columns 1-2, and page 866). The specification does not provide sufficient guidance that the expression of any level of anyone connexin family member in any type of cardiac cell would have any effect on cardiac conductance. In view of the different biological properties of the connexin family members, the complex interactions between the family members that results in gap formation and cellular coupling, and the differential cellular distribution of the connexin family members, the skilled artisan would not have been able to predict whether the introduction of any connexin family member into any cardiac cell would result in any effect on cardiac conduction.

With due respect, applicants draw the Examiner to their specification starting at the bottom of page 22 and top of page 23 wherein the provide guidance to proper usage of these proteins for treatment of disease.

> "Determing the appropriate conduction protein genetic material, i.e., determining which connexin protein is appropriate, is dependent upon which protein is appropriate, is dependent upon the particular cardiac conduction disturbances diagnose. For example, if the cardiac conduction pathway is a heart block or bradycardia, in which conductance is slowed or non-existant, Cx43 or Cx40, the faster connexins, is preferably used. However, if the cardiac conduction pathway disturbance is tachycardia, in which conductance is too rapid, Cx45 is preferably used."

In this passage Applicants teach where to use the appropriate connexin in a particular disease state. Similarly, applicants discusses on page 9, at the bottom of the page, further discussion of the use of the appropriate connexin not only in the appropriate disease but also the location of the targeted tissue.:

> "The specific gap junction protein chosen is dependent upon the nature of the identified problem. For example, where the conduction is slow or non-existent, such as in heart block or bradycardia, introduction of Cx40 or Cx43 would enhance conduction. In contrast, introduction of the slower conducting Cx45 into the AV node and His tissues would result in the prevention of brady-tachy syndrome and tachycardia."

Applicants specification teaches often those thing that Examiner suggests it does teach. Further, it is Applicants invention that provides the mapping capabilities with the delivery that actual testing of the target tissue is able to be determined before and after delivery, as well as to ongoing monitor the performance of the transfection. Note, in applicants specification they also teach leaving behind after transfection, a sensing electrode. This enables continue monitoring of the tissue after transfection. The examiner should be able to appreciate the significance of such a delivery system, that is novel, enabled, and inventive over the art.

Applicants respectfully request reconsideration of the amended claims in view of what is know in the art, and their contribution to the art, and respectfully submit their claims are enabled and cover patentable subject matter.

(2) Claims Rejections – 35 USC § 103

The Examiner maintain her rejection of claims 1, 4-9, 12-14, 24-25, 39-42 under 35 U.S.C. 103(a) over Mulier et al. in view of Leiden et al. and Kanter et al. Essentially the rejection was maintained since the applicant's delivery system as claimed does not recite the limitation that the delivered genetic material has any effect on the cardiac tissue. As such the combination of references cited provides motivation for using the catheter system taught by Mulier to deliver genetic material to cardiac tissue as taught by Leiden. Further, the skilled artisan would not consider the presence of tissue damage near the site of administration of genetic material as an obstacle to the transfection of nearby living cells. Therefore, as the limitation that the delivered genetic material must have a therapeutic effect on cardiac conduction is not recited by the instant claims, the applicant's arguments are not found persuasive and the rejection is therefore maintained.

Applicants traverse in part, and submit amended claims. Applicants traverse on the issue that the combination of references actually teach all elements of applicants claimed invention. No where does this combination of references provide the essential mapping feature or recognize that such feature is essential to have an effective transfection/transduction strategy. As to the other part of the Examiner's rejection indicating that the invention does not recite a limitation that the delivered genetic material has any effect on the cardiac tissue applicants have indicated that the delivered material transfects the local cells. Although this is not does not appear to directly be a 103 issue, applicants believe under 112 considerations it is necessary to tie the elements of the invention together.

Applicants respectfully request reconsideration and removal of the present rejection under 35 USC §103 in view of the submitted arguments and amendments.

Respectfully submitted,

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